REMARKS

Amendments

Claim 2 is amended to more properly use the article "the" in front of the second reference to the foreign ligand, and to expressly state the implicit connection between the "determining" step and the antecedent "comparing" step. Claim 6 is canceled because its limitation was already inherent in antecedent claim 2. This amendment does not alter the scope or subject matter of the claims, and introduces no new matter.

35USC103(a)

Prior descriptions (including Fesik, WO97/18471) of "SAR by NMR" wherein structure-activity-relationships are obtained by NMR, have invariably targeted "druggable" proteins, apo-proteins structurally characterized to have preformed ligand binding pockets, proteins such as FKBP, stromelysin, E2 DNA binding domain, Erm methyltransferase, SH2 domains, etc.

In contrast, the recited PAS domains are determined to be absent any ligand binding pocket, and such proteins have not been, and would not have been screened for core ligand binding by NMR because based on their structure, they were not expected to bind core ligands. Further, these domains do not require protein chaperones or other cellular components to adopt a stable fold, nor do they have known ligands. Finally, PAS domains are involved in protein/protein interactions (PPIs), making them members of a class of targets that are widely considered "undruggable":

> Of the roughly 30,000 unique protein sequences that comprise the human proteome, only 1% have been successfully targeted with small-molecule drugs. Moreover, most of those fall into the same few structural or functional families, the two most common being enzymes and G-protein-coupled receptors (GPCRs). These successfully targeted proteins typically share the property that the natural substrates or ligands with which they interact are themselves small organic molecules such as metabolites and neurotransmitters. Historically there has been notably little success in developing drug-like inhibitors of proteins whose natural ligands are other proteins. Screening of such targets against pharmaceutical company compound libraries has rarely produced useful hits or leads (Fig. 1). Consequently, these protein-protein interaction (PPI) targets have come to be considered as intractable with respect to small-molecule drug discovery, or

'undruggable' in industry jargon.
Whitty et al. Nature Chemical Biology 2, 112-118 (2006), p.112, first para).

Our claims are specifically directed to a method of detecting binding of a PAS domain of a protein with a foreign core ligand of the PAS domain, wherein the PAS domain is prefolded in its native state. The method specifically requires the steps of: (a) determining from NMR analysis of the PAS domain that the PAS domain comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity; (b) detecting a first NMR spectrum of the PAS domain in the presence of a foreign ligand; (c) comparing the first NMR spectrum with a second NMR spectrum of the PAS domain in the absence of the ligand; and (d) determining the presence of the ligand specifically bound within the hydrophobic core of the PAS domain.

As explained in our Specification some members of the PAS family are known to contain small molecule cofactors within their cores, and these cofactors are reportedly required for proper folding and functioning of the PAS domain within the context of the holo-protein. Specification, p.1, line 22 - p.2, line 1. However, for most PAS domains there is no evidence for such a cofactor. In fact, structurally characterized PAS domains without bound cofactors (Amezcua et al., 2002; Erbel et al., 2003; Morais Cabral et al., 1998) show tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site. Specification, p.2, lines 2-5.

Since the prior work provided no evidence of cofactors for most PAS domains, and taught that those limited PAS domains having cofactors required them for proper folding, and taught that PAS domains without cofactors had tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site, one skilled in the art would not have suspected that such PAS domains (without known cofactors and having tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site) would be rational candidates to screen for core ligand binding; in fact, the prior art teaches squarely away from such use.

Though the cited art does not support a prima facie case for obviousness, for good measure we provided affirmative evidence documenting the fact that one skilled in the art would have

considered the claimed invention nonobvious at the time it was made (see, Declaration of Professor Stephen Sprang, an expert in protein structure and dynamics).

We believe that the Action construes our claims more broadly than intended: emphatically, we are not claiming a method of detecting PAS domain binding by NMR. Rather, our claims are strictly limited to detecting PAS domain binding of a particular type of PAS domain – one determined to have no NMR-apparent a priori formed ligand cavity, to a particular type of ligand – a foreign, hydrophobic core ligand. This double-requirement underlies the nonobviousness of our claim: if one skilled in the art was motivated to detect PAS domain hydrophobic core ligand binding, the last place he would look is a PAS domain that he had already confirmed had no NMR-apparent a priori formed core ligand cavity.

The Final Action seeks to rebut the expert evidence of record with the Examiner's opinion, concluding that the expert's statements provide a "contradiction" and are "troubling to this examiner". The undersigned is not a recognized expert in NMR analysis of protein-ligand binding, and presumably, neither is the Examiner. However, Professor Sprang is a recognized expert, and so is applicant Professor Gardner a recognized expert, with over 20 years of experience studying proteins by NMR. To the eyes of an expert, the commentaries and conclusions of the Final Action are unwarranted and erroneous, and its analysis contains multiple and fundamental overstatements and technical inaccuracies. See Professor Gardner Declaration, attached.

Finally, to maintain an accurate record for review, we respectfully ask that the Examiner refrain from over- and misstating Applicant's statements. However self-congratulatory, it is factually erroneous to state that "appellant has not challenged the examiner [sic] position that … the prior art provides motivation and an assay to identify modulators". It is factually erroneous to state that "applicants stipulate that the prior art … provides motivation to identify modulator [sic]of the PAS domain, and functional assay [sic] to identify said modulator." To the contrary, the prior art squarely teaches that it would be futile and irrational to search for the subject

modulators (foreign core ligands) where the PAS domain is pre-confirmed to have no NMR-apparent a priori formed ligand cavity. Functional assays for protein-protein (PAS-PAS) interactions are not the same as foreign core ligand binding assays.

Please charge our Deposit Account No.19-0750 (order UTSD:1510) all necessary fees for this communication.

Respectfully submitted,
SCIENCE & TECHNOLOGY LAW GROUP

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Enc. Professor Gardner Declaration under 37CFR1.132

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